UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/095,536	06/10/98	KINK J	OPHD-03282

EXAMINER	
HAMUD, F	
ART UNIT	**PAPER NUMBER**
1646	8

DATE MAILED: 12/22/99

HM12/1222

VIRGINIA S MEDLEN
MEDLEN AND CARROLL
SUITE 2200
220 MONTGOMERY STREET
SAN FRANCISCO CA 94104

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File copy

Office Action Summary

Application No.	Applicant(s)
09/095,536	John A. Kink
Examiner	**Group Art Unit**
Fozia Hamud	1646

☒ Responsive to communication(s) filed on *Dec 7, 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6, 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claim 1 has been amended in Paper No.5, filed on 10/7/99. Thus amended claim 1 and original claims 2-18 are pending and under consideration.

2. Receipt of Applicant's arguments and amendments filed in Paper No.5, 10/7/99 is acknowledged.

3. the following previous objections and rejections are withdrawn in light of Applicants amendments filed in Paper No.5, 10/7/99:

I. The rejection of claims 1-6 made under 35 U.S.C. §101.

ii. The rejection of claim 1 made under 35 U.S.C. §112, second paragraph.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Applicant's arguments filed in Paper No.5, 10/7/99, have been fully considered but were deemed persuasive in part. The issues remaining are restated below.

Claim Rejections - 35 USC § 103

6a. Claims 1-3, 7-15 are rejected under U.S.C. § 103 as being unpatentable over Starnes et al. (12/92) and Doherty et al (09/92).

This rejection is maintained for reasons set forth in pages 3-5 in Paper No.4 (July 2,1999). Applicant argues that references cited by the Examiner do not disclose all the elements of the claims, and that neither reference cited suggests a therapeutic composition comprising the antibodies as combined in the present invention, Applicant also argues that the cited references do not contain a suggestion or motivation to modify or combine teachings, and do not provide a

reasonable expectation of success should the combination of references be carried out. Applicant further argues that the Examiner disregarded the Applicant's failure data, and that literature indicates that "combination inhibitions" may be problematic.

Firstly, Starnes et al and Doherty et al, combined teach, that TNF-alpha (TNF-α), IL-6 and IFN-gamma (IFN-γ) all play important roles in septic shock, and that administration of antibodies directed against each cytokine considerably decreased the mortality of endotoxin shock. Thus, Starnes et al, and Doherty et al references combined, suggest that antagonizing all three cytokines (TNF-α, IL-6 and IFN-γ) may be beneficial to human subjects or animals with severe infections and may be useful in treating or preventing sepsis. Therefore, the two references taken together, would have suggested the instantly claimed invention. Although the two references do not disclose a composition comprising the antibodies as combined in the present invention, the two references demonstrated that antibodies against the above cited cytokines, individually, are effective against septic shock, therefore, combing antibodies against all three in one pharmaceutical composition would have been obvious to one of ordinary skill in the art. This position is consistent with the decision in In re Kerkhoven, which states "It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose". Furthermore, if each of Starnes et al, and the Doherty et al references disclosed each of the limitations of the claimed invention, this rejection would have been a 35 USC § 102 rejection, rather, a 35 USC § 102 rejection.

With respect to the argument that there is no reasonable expectation of success if the two references are combined, Starnes et al demonstrate that antibodies directed against TNF or IL-6 protected mice against lethal challenge of *E.coli* and bacterial lethality, (figure 4 on page 4188) and Doherty et al demonstrate that antibodies against IFN-γ protects against endotoxin lethality, (figure 3, on page 1667). One of ordinary skill in the art would have had a reasonable expectation of success to combine the disclosed antibodies for treatment against sepsis, absent any evidence to the contrary. With respect to Applicant's argument that the Examiner ignored Applicant's failure data, Doherty et al, demonstrate that mice treated with anti-IFN-γ antibodies had a dose-dependent improvement in survival from lethal doses of LPS (page 1667 and figure 3 on page 1667), the researchers also demonstrate that anti-IFN-γ antibodies protect mice from lethality induced by TNF-α, showing that all the mice pretreated with anti-IFN-γ antibodies survived compared to mice pretreated with nonimmune IgG, (page 1668, column 2). Therefore, prior art of record is enabling for a composition comprising anti-IFN-γ antibodies for the treatment of sepsis, and Examiner can not explain Applicant's failure data concerning anti-IFN-γ antibodies and sepsis.

With respect to Applicant's argument that literature indicates that "combination inhibitions" may be problematic, Applicant does not cite any research where the efforts to combine antibodies against TNF, IL-6 and IFN for the treatment of sepsis have failed or have had deleterious effects. Applicant cites Opal et al, who disclose that inhibition of both IL-1 and TNF results in exacerbation of the invasive infection and a rapidly lethal outcome. However, another reference submitted by Applicant, Russell et al, teach that inhibition of IL-1 and TNF are equally

effective as single-agent therapies in the prevention of lethality during endotoxemia, (page 1536, column 1). Russell et al, also demonstrate that during rigorous conditions of endotoxic shock, inhibition of both TNF and IL-1 provided greater protection against lethality and greater improvement in various organ dysfunctions than treatment with either inhibiting TNF or IL-1. Thus the two references (Russell et al, and Opal et al), disclose conflicting results concerning the effects of inhibiting both IL-1 and TNF on the lethality during endotoxemia, which may be explained, due to the dichotomous roles of IL-1 and TNF in the host response to invasive bacterial infection and also to the different animal models used by the researchers. Although the Opal et al reference teaches against simultaneous inhibition of certain cytokines, it has no disclosure concerning any deleterious effects that may be caused by the simultaneous inhibition of IL-6, TNF and IFN, therefore, this reference is irrelevant to the instant invention. Applicant must demonstrate that others have failed in their efforts to combine the antibodies against IL-6, TNF and IFN for the treatment of sepsis, and that only they have achieved unexpected results.

6b. Claims 1, 3-6 and 16-18, are rejected under U.S.C. § 103 as being unpatentable over Starnes et al. (12/92) and Doherty et al (09/92) in view of Emery et al (U.S. Patent 5,420,253). This rejection is maintained for reasons set forth in pages 5-6 in Paper No.4 (July 2,1999). Teachings and answer to arguments concerning Starnes et al. and Doherty et al references are set forth directly above, in 6a of this office action.

Emery et al reference teaches the production of avian antibodies by immunizing an egg-laying female bird with an antigen such as TNF, to stimulate the production of an IgG against TNF, (column 3, line 61 through column 4, line 67), and a method of administering said avian

antibodies by suppository (rectally), (column 8, lines 67-68). Emery et al reference is relied upon for it's disclosure of the advantages of producing avian antibodies, and since claims 1, 3-6 and 16-18 are rejected under 35 USC § 103 and not under 35 USC § 102, Emery et al reference does not have to disclose each and every limitation of the rejected claims.

Conclusion

7. No claim is allowed.

8 **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit1646
December 20, 1999.

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER